MEDICAL MANAGEMENT OF PEDIATRIC PATIENTS WITH MOYAMOYA ANGIOPATHY: Proceedings from the Pediatric Moyamoya Summit, Nov 7th, 2023

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Principles of Medical Management

The main risk of moyamoya angiopathy (MMA) in children is brain ischemia related to hypoperfusion through stenotic or occluded vessels, whereas the hemorrhagic risk is much lower in pediatric patients(1,2). Hence, the goal of medical management is to preserve brain perfusion to avoid stroke or transient ischemic attack (TIA). Antithrombotic treatment is added to prevent arterial ischemic stroke occurrence by thrombotic occlusion of a stenotic artery.

Measures and Precautions to Maintain Cerebral Hemodynamics

Compromised cerebral perfusion in children with MMA is associated with an increased risk of cerebrovascular events. Therefore, specific measures and precautions are recommended to be implemented both in daily life and during medical care for pediatric patients with MMA. These measures aim to avoid or rapidly treat hypotension, hypoxia, and cerebral vasoconstriction, which are known as main precipitating factors for arterial ischemic stroke or TIA(3). Patients, relatives, and the healthcare team must be informed of the importance of these measures through a patient card/letter, free-access guidelines to practitioners, or other means. A sample patient card is included as Supplement 1.

- **Sports, physical activities**: Ischemic events can be triggered by hyperventilation due to physical activity, prolonged crying, or playing wind instruments(3). Individual tolerance to physical activities is variable and limitations should be adjusted based on disease severity and the patient's reports(4). Adequate hydration prior to physical activity is recommended. The authors suggest avoidance of vigorous physical activity in extreme heat.
- **Altitude, plane travel**: Relative hypoxia at altitude or lower air pressure combined with relative dehydration during flight travel may trigger TIA or stroke. Gradual rise in altitude for mountain journeys and initial short-distance flights may help to estimate individual tolerance.
- **Management of illness**: Pediatric MMA patients are particularly vulnerable to dehydration induced by gastro-intestinal infection, fever, or recurrent vomiting. Measures to maintain adequate hydration should be implemented early, including intravenous fluid rehydration, especially in younger children.
- **Drug prescription:** Hypertension correction should be very cautious as

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patients may rely on hypertension to maintain adequate cerebral perfusion. Vasoconstrictive medications, such as anti-migraine vasoconstrictors (triptans, ergotamine dihydrate), and local (nasal) vasoconstrictors, are contraindicated. Oral estrogens are usually contraindicated in patients with a history of stroke.

- **Local and general anesthesia**: Locally injected epinephrine may have a systemic effect on blood pressure, heart rate and the frequency of premature ventricular contractions (5), with a theoretical cerebral risk in these patients given their impaired cerebrovascular reactivity. Local anesthesia, for example for oral surgery or tooth extraction should take this into account. General anesthesia often induces a significant systemic pressure decrease, especially at induction. Pediatric MMA patients should be anesthetized with a specific protocol to avoid hypotension, including IV fluid before anesthesia induction, close blood pressure monitoring during anesthesia, and blood loss compensation (6). Maintaining normocarbia is also important to limit vasodilation and vasoconstriction. These measures are applicable even for minor surgery, whatever the duration of anesthesia. Additional intraoperative and anesthetic management considerations are reviewed elsewhere(6–8).
- **Procedures:** To prevent crying and hyperventilation, non-pharmacological approaches or premedication are recommended in anxious patients(7). Control of nausea and vomiting is also important(9).
- **Temperature considerations:** Fever, overheating, hot or spicy food intake, and cold exposure can increase hemodynamic stress and trigger MMA symptoms and should be adequately managed in these patients (3,10–13).

Electroencephalography (EEG) is often employed in patients with moyamoya due to high risk of seizures in this population. Hyperventilation, often used as a provocation technique for children with suspected epilepsy, should be avoided in patients with moyamoya due to the risk of hypocapnia-induced vasoconstriction and consequent provocation of ischemic events(14).

Antithrombotic Therapy

Anti-thrombotic therapy (ATT) plays an important role in the management of patients with MMA(15). Anti-platelet medications, such as aspirin and clopidogrel, are the most commonly used anti-thrombotics in children(16). These medications are used to prevent the formation of thrombi that may occlude stenotic arteries(1). The use of ATT is often extrapolated from general stroke prevention strategies for infants and children(17) and generally lacks conclusive evidence of efficacy(18,19). More recently, a systematic review evaluated 9 adult studies enrolling 16,186 patients with MMA(20), revealing that anti-platelet therapy did not reduce the risk of ischemic stroke but was associated with a reduced risk of hemorrhagic stroke. A single retrospective, population based, longitudinal cohort of 25,978 adult MMA patients suggested that anti-platelet therapy was associated with an improvement in survival(21). Nevertheless, the applicability of such data to a pediatric cohort requires evaluation.

Pragmatically, aspirin (3-5 mg/kg/day, up to adult dosing) is often initiated, unless contraindicated, with careful clinical and radiologic monitoring to inform on addition of or substitution with a second anti-platelet agent.

Specific therapeutic choices are often heavily influenced by institutional protocols. Anti-platelet treatments are often continued long-term even after neurovascular interventions to prevent thrombotic occlusion of both the native stenotic and collateral vessels and the surgical collateral vessels.

Perioperative Management

Many children with MMA undergo surgical revascularization to decrease their long-term stroke risk. However, perioperative ischemic events, typically occurring within the first week after surgery, complicate around 10% of cases.(22–24) Younger age, steno-occlusive disease involving the posterior circulation, higher Suzuki stage, history of stroke, and frequent TIAs are risk factors for perioperative ischemic complications.(25,26) Perioperative medical management, which aims to mitigate this high stroke risk, focuses on the key tenets below(8,9).

- **Maintaining adequate cerebral perfusion**, which allows for oxygen and nutrient delivery to brain tissue, is achieved by maintaining euvolemia and avoiding hypotension. Preoperatively, high-risk children may be admitted for intravenous hydration with isotonic fluids.(6) During and after surgery, avoidance of both hypertension (which increases risk for bleeding at the surgical site or from fragile moyamoya collateral vessels) and hypotension (which could provoke cerebral ischemia) is critical. Experts recommend keeping blood pressure at or above the patient's baseline, administering intravenous fluids for hypotension, and considering vasopressors for fluid-refractory hypotension.(6) Minimizing fluctuations in carbon dioxide is also important to decrease risk of cerebral vasoconstriction, which could decrease cerebral perfusion, or vasodilation, which could result in a steal phenomenon due to preferential vasodilation of healthy vasculature.
- **Preserving adequate blood oxygenation and glucose content** is crucial, as children with moyamoya angiopathy have limited capacity for compensatory vasodilation. In children with sickle cell disease, exchange transfusion in the week preceding neurosurgery is recommended.(27) Even in children with moyamoya without sickle cell disease, anemia has been identified as a modifiable risk factor for perioperative stroke(24,28), though there is equipoise about optimal transfusion thresholds (29). Patients with MMA may benefit from higher transfusion thresholds compared with other neurosurgical patients due to higher vulnerability to cerebral ischemia in the setting of decreased cerebral perfusion and autoregulatory capacity. Experts recommend keeping oxygen saturations above 95%.(6) Maintaining normoglycemia is likewise important to ensure adequate glucose delivery to brain tissue.
- **Minimizing metabolic demand**, such as by maintaining normothermia and promptly treating seizures, mitigates stroke risk by decreasing the need for oxygen and nutrients. Experts do not recommend antiseizure medications in all patients, but home maintenance antiseizure medications should be continued in the perioperative period without interruption.(6) Prompt recognition and aggressive treatment of fevers is recommended during the perioperative period.

- **Antiplatelet therapy** In the absence of significant surgical bleeding complications, continuation of antiplatelet therapy without interruption perioperatively is recommended to prevent thromboembolic complications.(6)
- **Perioperative pain and agitation control** are crucial. Crying/agitation may lead to hyperventilation and hypocarbia-associated cerebral vasoconstriction, and this phenomenon can provoke TIA and stroke. Nausea control has been shown in a retrospective cohort to decrease risk of perioperative stroke.(9) Treatment of pain, agitation, and nausea should preferably have minimal effect on blood pressure and preserve the neurologic examination.
- **Additional considerations** depend on the type of surgical approach. For example, children who undergo direct revascularization are at higher risk for cerebral hyperperfusion postoperatively, though this risk is lower in children compared with adults.(30)

Acute Stroke Management

The above mentioned measures also apply to acute stroke management, as stroke mechanism in this condition is mostly related to compromised cerebral hemodynamics. In addition to the above and general neuroprotective care, positioning the head of bed flat to augment cerebral perfusion is reasonable, at least in the acute setting before significant cerebral edema necessitates otherwise. Previously diagnosed MMA is typically considered a contraindication to thrombolytic therapy and mechanical thrombectomy due to high risks and likely low benefit of these hyperacute therapies in this population.

FOLLOW UP

Rehabilitation and Neurodevelopmental Follow-Up

While the mainstay of treatment of MMA is surgical, a robust rehabilitation program for patients with MMA and ischemic or hemorrhagic stroke may help ameliorate accompanying neurologic deficits, although data to support this are sparse. It is important to note that outcomes in children with moyamoya may differ from those in children with other causes of stroke given the distribution of their ischemic injury as well as the high rate of stroke recurrence, silent infarction, chronic hypoperfusion, and comorbid medical and neurologic conditions (31–33). Children with MMA are at risk of motor impairments (34), neurocognitive deficits, including impaired intelligence and executive functioning, even in the absence of a clinical stroke (35), and epilepsy (36), suggesting the importance of a multidisciplinary approach to rehabilitation. Like children with stroke from other causes, deficits may emerge and new rehabilitation needs may be identified as children grow and experience increased physical and cognitive demands(37). The earlier such deficits can be identified, the earlier rehabilitative interventions and supports that target those deficits can be put in place(38,39), emphasizing the importance of close neurodevelopmental follow-up in the long-term management of patients with moyamoya, even after surgical revascularization.

Imaging Follow-up

Standard imaging with MRI-MRA and/or DSA aims to assess for new ischemic injury, progression of steno-occlusive disease in

affected territories, and new vascular stenosis in previously unaffected regions (15). Initially, some patients with MMA may present with unilateral disease. However, one must remain vigilant and monitor for development of vasculopathy on the contralateral side with serial vascular imaging. A Japanese study of 93 patients with unilateral moyamoya found that almost a quarter of patients developed contralateral involvement over a mean of 72 months. Notably, children were at significantly higher risk (HR 7.21, $p < 0.001$) than adults of developing contralateral progression(40). In Asian populations, children with the founder RNF213 R4810K variant also seem to be at higher risk for development of contralateral disease(40,41). Risk of contralateral progression is also present for adults of Caucasian descent, with one study reporting 17.4% of adults with initially unilateral MMA developing contralateral disease over a mean follow up time of 5.4 years(42). In addition to monitoring for contralateral involvement, surveillance imaging aims to evaluate for new or progressive posterior circulation involvement. A recent study of adults and children with MMA found that 12.6% of patients had new or progressive posterior circulation disease on follow up imaging(43). With a lack of data regarding evaluation and management protocols for MMA in children the timing of follow-up assessments should be individualized (15).

Advanced imaging modalities may provide further information concerning brain perfusion or cerebrovascular reserve assessment. Cerebral perfusion assessment in MMA may be utilized in the preoperative evaluation to aid in surgical decision-making and after revascularization to monitor the perfusion changes (44,45). MR perfusion techniques are currently the most widely used in the pediatric setting and include dynamic susceptibility contrast perfusion (using gadolinium to gauge relative perfusion changes) and arterial spin labeling perfusion (using endogenous water tracer) (46–51). Other perfusion techniques include 99mTechnecium-labeled Single Photon Emission Computed Tomography and 15O-water Positron Emission Tomography, with the drawback of ionizing radiation exposure (52–55). Cerebrovascular reserve capacity, assessed through acetazolamide or CO2 challenge, is reported as a predictor of ischemic events and a prognostic factor (56), but its use in the pediatric setting is not well established.

Specific Follow-Up According to Genetic Cause

Each monogenic cause linked to moyamoya presents distinct characteristics, yet comprehensive data on the natural progression and course of moyamoya within each genetic syndrome remains largely elusive. Management of these patients should consider both cerebrovascular and peripheral vascular system involvement, alongside associated comorbidities, which influence therapeutic decisions (Table 1). Thus, children with monogenic moyamoya necessitate tailored, multidisciplinary management, including detailed clinical, laboratory and imaging assessments. A thorough three-generation family history is essential, particularly when there is history of consanguinity or multiple affected individuals, suggesting Mendelian inheritance. While family screening is generally not recommended for RNF213-related disease due to low penetrance and lack of data on the natural history and risk for stroke/hemorrhage in asymptomatic patients, it may be considered in selected cases.

TABLE 1

Mutated Genes/ Genetic Syndrome	Considerations
YY1AP1, GUCY1A3, SMARCAL1, MYH11, ANO1	Monitor for posterior cerebral artery involvement (43,57–61)
Neurofibromatosis type 1, Alagille syndrome, *RNF213, YY1AP, CHD4*	Surveil for hypertension due to renal artery disease or aortic disease (including mid-aortic syndrome) (57,62–65)
ACTA2, RNF213, SMARCAL1, PCNT, CHD4, BRCC3/MTCP1 deletion, Down syndrome	Assess the pulmonary and coronary arteries (59,62,66–68)
Neurofibromatosis type 1, *RNF213, ACTA2, SAMHD1, YY1AP1, PCNT, ANO1*	Monitor for cerebral or peripheral aneurysms (57,61,69–72)

Transition to Adult Follow-Up

Carefully planned transition to adult care ensures continued monitoring for disease progression and prevention/management of traditional vascular risk factors that could jeopardize collateral blood flow. As patients age, intracranial hemorrhage becomes a more frequent MMA manifestation; whether to discontinue aspirin in adulthood remains unknown. The morbidity and mortality associated with hemorrhage is substantial, with 7% and 30% rates of death for initial and recurrent bleeding, respectively. Precipitating factors may include hypertension, degenerative changes within collateral vessels, or pregnancy, although a recent review of the risk of moyamoya-related neurologic events during pregnancy, delivery, and postpartum demonstrated similar or lower risk than what was suggested by natural history studies (73). Given the continued risk of ischemic events and significant hemorrhage in young adults with MMD, it is critical to assure continuity of care.

Conclusions

In combination with appropriate surgical management, medical management of pediatric MMA aims to prevent stroke and TIA by maintaining adequate cerebral perfusion, preventing thrombotic complications, and ensuring cerebral metabolic capacity meets demand. The perioperative period is a particularly high-risk time for ischemic complications, necessitating careful medical management orchestrated by a multidisciplinary expert team. Long-term clinical and radiographic follow up is critical and may be guided, in part, by underlying genetic and non-genetic conditions.

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